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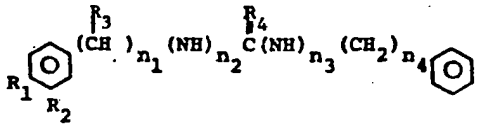
GB 0715341
Chemical Abstracts, Vol 100(25), No 203126b
Chemical Abstracts, Vol 103(15), No 23132x
Chemical Abstracts, Vol 97(3), No 23536w

(58) Field of search
C2C

(54) Amides and compositions thereof having anti-inflammatory and analgesic activity

(57) Substituted aromatic ω-araalkanamide compounds, and pharmaceutically-acceptable salts thereof, of the formula:



wherein n_1 is 0 or 1, n_2 is 0 or 1, n_3 is 0 or 1, n_4 is an integer between 0 and 12, $n_2 + n_3 = 1$, R_1 is selected from the group consisting of H, OH, and a short-chain ester, R_2 is selected from the group consisting of H, OH, OCH_3, and OCH_2CH_3, R_3 is H or CH_3, and R_4 is O or S.

GB 2 168 975 A

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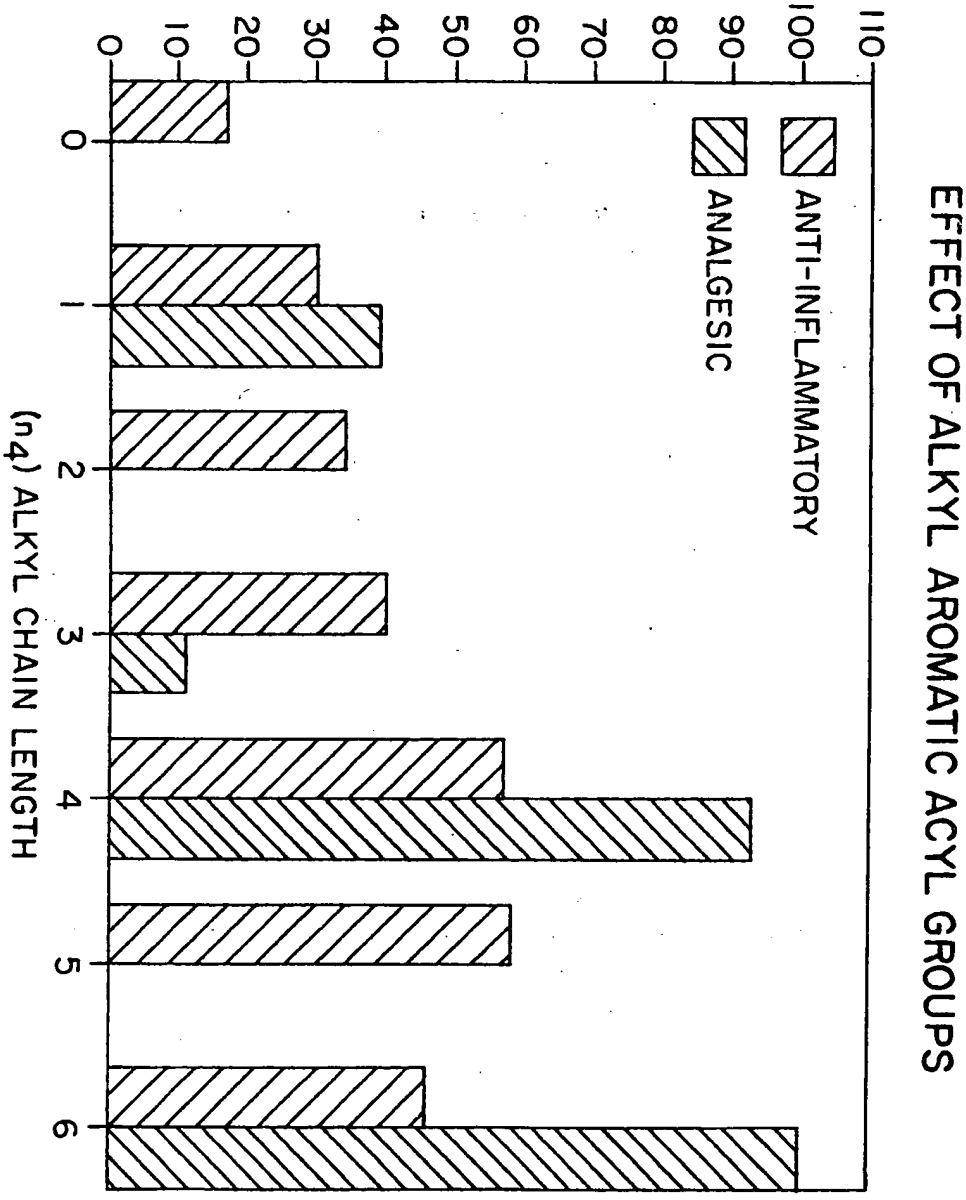
EFFECT OF ALKYL AROMATIC ACYL GROUPS
% INHIBITION
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ANTI-INFLAMMATORY
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1
2
3
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5
6
(n4) ALKYL CHAIN LENGTH

SPECIFICATION

Compounds and compositions having anti-inflammatory and analg sic activity

Technical field

The present invention relates to certain araalkanamides and pharmaceutical compositions containing these compounds which exhibit anti-inflammatory and analgesic activity.

Background of the invention

Inflammation, or the "inflammatory response", is the result of complex interconnected physiological events, including increased vascular permeability, fluid accumulation, and the migration of a changing population of inflammatory cells into the inflammed area. The clinical manifestations of inflammation include swelling (edema), increased local temperature, erythema, and pain. The inflammatory response can be triggered by way of a number of causative factors, including certain bacteria, radiation, hypersensitivity to chemical agents, arthritis-like conditions, and the like. The inflammatory response is generally believed to be a primary defense mechanism in the body, but, unchecked, can become excessive and can result in functional impairment.

The use of non-steroidal anti-inflammatory, anti-pyretic and analgesic drugs, especially the salicylates, which include aspirin and aspirin derivatives, to combat inflammation and attendant pain is accepted medical practice. The non-steroidals are commonly employed to relieve pain and inflammation associated with, for example, bursitis, arthritis, and the like.

While "pain" is incapable of precise definition due to its basically subjective nature, it can generally be said that the term refers to feelings of distress or suffering caused by stimulation of specialized nerve endings. A great variety of drugs have been developed to reduce pain in man and other animals; some directed to eliminating pain at its source, and others directed to blocking the assimilation of pain by the brain. Among the latter group of drugs that are designed to block the sensation of pain, are the analgesics, which generally relieve pain without causing unconsciousness. Analgesics can be further classified in two main categories: opioid analgesics, including morphine, codeine, levor-phanol, and the morphine-like analgesics merperidine, and methadone; and antipyretic analgesics, such as aspirin, phenacetin, acetaminophen, phenylbutazone, and indomethacin.

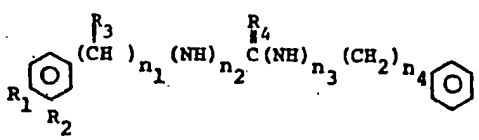
The antipyretics are weak analgesics, with much of their effect in the peripheral nervous system, so that behavioral changes do not usually occur. Generally, these analgesics are used to relieve somatic pain originating from muscles, joints, tendons and fasciae.

It has been recently discovered that capsaicin, a natural product of certain species of the genus *Capsicium*, induces analgesia. Capsaicin (8-methy-N-vanillyl-6-nonenamide) and "synthetic" capsaicin (N-vanillylnonamide) are disclosed as analgesics in U.S. Patent 4,313,958, LaHann, issued February 2, 1982. Analgesic activity of capsaicin has also been discussed in the chemical and medical literature, including Yaksh, et al, *Science, 206*, pp 481-483 (1979); Jansco, et al, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, Vol. 311, pp 285-288 and Holzer et al, *Eur. J. Pharm.* Vol. 58, pp 511-514 (1979). U.S. Patent 4,238,505, Nelson, issued December 9, 1980, discloses 3-hydroxyacetanilide for use in producing analgesia in animals. European Patent Application 0089710, LaHann, et al, published September 28, 1983, describes hydroxyphenylacetemides with analgesic and anti-irritant activity. Similarly, analgesic and anti-irritant activity is disclosed for N-vanillyl sulfonamides in U.S. Patent 4,401,663, Buckwalter, et al, issued August 30, 1983; N-vanillylureas in European Patent Application 0068590, Buckwalter, et al, published January 5, 1983; N-(substituted phenyl)methyl alkynamides in U.S. Patent Application Serial No. 514,204, Janusz, et al, filed July 14, 1983; methylene substituted N-(substituted phenyl)methylalkanamides in U.S. Patent Application Serial No. 514,205, Janusz, et al, filed July 14, 1983; N-(substituted phenyl)methyl-cis-monounsaturated alkenamides, in U.S. Patent Application Serial No. 514,206, LaHann, et al, filed July 14, 1983; and N-(substituted phenyl)methyl diunsaturated amides in U.S. Patent Application Serial No. 514, 207, LaHann, et al, filed July 14, 1983. None of these documents suggests in any way that the disclosed compounds have anti-inflammatory activity.

It has now been discovered that certain araalkanamides have anti-inflammatory and analgesic activity similar to that of non-steroidal analgesics such as aspirin in human and lower animals. These araalkanamides are far less toxic than capsaicin.

Summary of the invention

The present invention provides compounds useful for reducing inflammation and producing analgesia in humans and lower animals, of the formula:



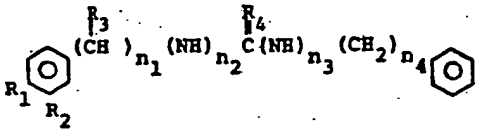
wherein n_1 is 0 or 1, n_2 is 0 or 1, n_3 is 0 or 1, n_4 is an integer between 0 and 12, $n_2 + n_3 = 1$, R_1 is selected from

the group consisting of H, OH, and a short-chain ester, R_2 is selected from the group consisting of H, OH, OCH_3, and OCH_2CH_3, R_3 is H or CH_3, and R_4 is O or S; and pharmaceutically-acceptable salts thereof.

This invention also provides pharmaceutical compositions comprising a safe and effective amount of these compounds, or mixtures thereof, and a pharmaceutically-acceptable carrier. Also provided are methods for reducing inflammation and producing analgesia by administering the compounds and compositions of this invention.

Description of the invention

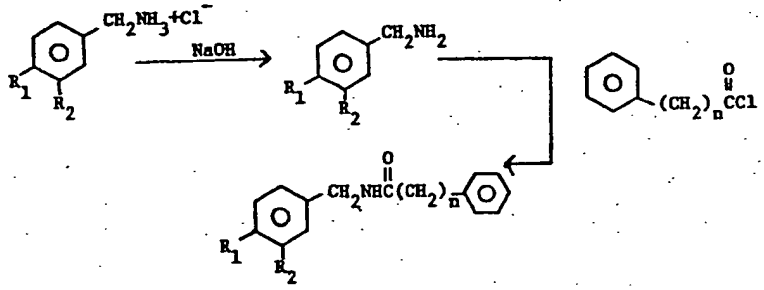
The compositions and methods of this invention incorporate certain substituted aromatic ω-araalkanamides, or pharmaceutically-acceptable salts thereof, of the formula:



wherein n_1 is 0 or 1, n_2 is 0 or 1, n_3 is 0 or 1, n_4 is an integer between 0 and 12, $n_2 + n_3 = 1$, R_1 is selected from the group consisting of H, OH, and a short-chain ester, R_2 is selected from the group consisting of H, OH, OCH_3, and OCH_2CH_3, R_3 is H or CH_3, and R_4 is O or S.

Preferably, n_1 is 1, n_2 is 1, n_3 is 0, n_4 is an integer between 0 and 8, R_1 is OH or a short-chain ester, R_2 is OH or OCH_3, R_3 is H, R_4 is O. Most preferably, R_1 is OH, R_2 is OCH_3, and n_4 is an integer between 0 and 6. As is evident from the figure showing the results of Example VI, preferred values of n_4 for anti-inflammatory activity, in descending order, are $n_4=5$, $n_4=4$, $n_4=6$, $n_4=3$, $n_4=2$, and $n_4=1$. Preferred values of n_4 for analgesic activity, in descending order are, $n_4=6$, $n_4=5$, and $n_4=4$. Araalkanamides preferred for anti-inflammatory activity, in descending order, are N-vanillyl-6-phenylhexanamide, N-vanillyl-5-phenylpentanamide, N-vanillyl-7-phenylheptanamide, N-vanillyl-4-phenylbutyramide, N-vanillyl-3-phenylpropanamide, and N-vanillyl-2-phenylethanamide. Araalkanamides preferred for analgesic activity, in descending order, are N-vanillyl-7-phenylheptanamide, N-vanillyl-6-phenylhexanamide, and N-vanillyl-5-phenylpentanamide. Preferred araalkanamides include those derived from ω-phenyl ethamoic, propanoic, butanoic, pentanoic, hexanoic and heptanoic acid. Preferred pharmaceutically-acceptable araalkanamide salts include the sodium, potassium, calcium, magnesium, and ammonium salts.

The aralkanamides described herein can be readily prepared by the following typical synthetic scheme:



The acids used in the synthesis of preferred araalkanamides are commercially-available.

Compositions

The compositions of the present invention comprise:

(a) a safe and effective amount of an araalkanamide defined herein; and

(b) a pharmaceutically-acceptable carrier.

A safe and effective amount of araalkanamide is that amount which provides anti-inflammatory activity and analgesia, thereby alleviating or preventing the inflammation or pain being treated at a reasonable benefit/risk ratio, as is intended with any medical treatment. Obviously, the amount of araalkanamide used will vary with such factors as the particular condition that is being treated, the severity of the condition, the duration of the treatment, the physical condition of the patient, the nature of concurrent therapy (if any), the route of administration, the specific formulation and carrier employed, and the solubility and concentration of araalkanamide therein.

Depending upon the particular route of administration, and compatibility with the active chosen, a variety of pharmaceutically-acceptable carriers, well-known in the art, may be used. These include solid or liquid fillers, diluents, hydrotropes, excipients, surface-active agents, and encapsulating substances. The amount of the carrier employed in conjunction with the araalkanamide is sufficient to provide a practical quantity of material per unit dose.

Pharmaceutically-acceptable carriers for systemic administration that may be incorporated into the

compositions of this invention, include sugars, starches, cellulose and its derivatives, malt, gelatin, talc, calcium sulfat , vegetable oils, synthetic oils, polyols, alginic acid, phosphate buffer solutions, emulsifiers, isotonic saline, and pyrogen-free water. Specific pharmaceutically-acceptable carriers are described in the following U.S. Pat nts and European Patent Applications, all incorporated by reference herein: U.S. Patent 4,401,663, Buckwalter, et al, issued August 30, 1983; European Patent Application 0089710, LaHann, et al, published September 28, 1983; and European Patent Application 0068592, Buckwalter, et al, published January 5, 1983. Preferred carriers for parenteral administration include propylene glycol, ethyl oleate, pyrrolidone, ethanol, and sesame oil. Preferably the pharmaceutically-acceptable carrier, in compositions for parenteral administration, comprises at least about 90% by weight of the total composition.

Various oral dosage forms can be used, including such solid forms as tablets, capsules, granules and bulk powders. These oral forms comprise a safe and effective amount, usually at least about 5%, and preferably from about 25% to about 50% of the araalkanamide. Tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated or multiple compressed, containing suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, preservatives, flow-inducing agents, and melting agents. Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules, containing suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, melting agents, coloring agents, and flavoring agents. Preferred carriers for oral administration include gelatin, propylene glycol, cottonseed oil and sesame oil. Specific examples of pharmaceutically-acceptable carriers and excipients that may be used to formulate oral dosage forms, which may be used in formulating oral dosage forms containing araalkanamides, are described in U. S. Patent 3,903,297, Robert, issued September 2, 1975, incorporated by reference herein. Techniques and compositions for making solid oral dosage forms are described in Marshall, "Solid Oral Dosage Forms," *Modern Pharmaceutics, Vol. 7*, (Banker and Rhodes, editors), 359-427 (1979), incorporated by reference herein.

The compositions of the present invention can also be administered topically to a biologic subject, i.e, by the direct laying on or spreading of the composition on epidermal or epithelial tissue. Such compositions include lotions, creams, solutions, gels and solids. These topical compositions comprise a safe and effective amount, usually at least about 0.5%, and preferably from about 1% to about 5%, of the araalkanamide. Suitable carriers for topical administration of the araalkanamide preferably remain in place on the skin as a continuous film and resist being washed off easily by perspiration or by immersion in water. Generally, the carrier is either organic in nature or an aqueous emulsion and capable of having the araalkanamide dispersed or dissolved therein. The carrier may include pharmaceutically-acceptable emollients, coloring agents, fragrances, emulsifiers, thickening agents, and solvents.

Specific systemic and topical formulations useful in this invention are described in the following U.S. Patents and European Patent Applications, all incorporated by reference herein: U.S. Patent No. 4,401,663, Buckwalter, et al, issued August 30, 1983; and European Patent Application 0089710; LaHann, et al, published September 28, 1983; European Patent Application 0068590, Buckwalter, et al, published January 5, 1983; and European Patent Application 0068592, Buckwalter, et al, published January 5, 1983. Topical vehicles, useful herein, are disclosed in the following U.S. Patent Applications, incorporated by reference herein: "Improved Penetrating Topical Pharmaceutical Compositions Combining l-dodecylazacycloheptan-2-one", Serial No. 506,275, Cooper, filed June 21, 1983; and "Penetrating Topical Pharmaceutical Compositions Containing N-(2-hydroxyethyl)-pyrrolidone", Serial No. 506,273, Cooper, filed June 21, 1983. Additional formulations, useful for parenteral, oral and topical administration of araalkanamides, are disclosed in the following U.S. Patent Applications all incorporated by reference herein : "Compositions Useful for Producing Analgesia", Serial No. 514,206, LaHann and Buckwalter, filed July 14, 1983: "Novel Compounds and Compositions Useful for Producing Analgesia", Serial No. 514,207, LaHann, Janusz, and Buckwalter, filed July 14, 1983; "Novel Compounds Useful for Producing Analgesia", Serial No. 514,204 Janusz and LaHann, filed July 14, 1983. and "Novel Compounds and Compositions Useful for Producing Analgesia", Serial No. 514,205 Janusz, Buckwalter and LaHann, filed July 14, 1983.

Methods for producing anti-inflammatory activity and analgesia

The present invention also encompasses methods of producing anti-inflammatory activity and analgesia in humans or lower animals through administering, to the human or lower animal, a safe and effective amount, usually from about 1 mg to about 3600 mg per day, preferably from about 200 mg to about 2000 mg per day, of an araalkanamide. While dosages higher than the foregoing are effective to reduce inflammation and produce analgesia, care must be taken in some individuals to prevent adverse side effects. The araalkanamides and compositions of this invention can be used to treat and prevent pain, to provide analgesia, and to reduce inflammation in various disorders at the deeper structures, muscles, tendons, bursa and joints associated with disease and trauma, and in various other conditions in which non-steroidal anti-inflammatory, anti-pyretic and analgesic drugs such as aspirin have heretofore been used to alleviate pain and discomfort and reduce inflammation.

The araalkanamides and compositions of the instant invention can be administered topically or systemically. Systemic application includes any method of introducing the araalkanamide compound into the tissues of the body, e.g., intrathecal, epidural, intramuscular, transdermal, intravenous, intraperitoneal, subcutaneous, sublingual, and oral administration.

A preferred method of parenteral administration is through intramuscular injection. As is known and practiced in the art, all formulations for parenteral administration must be sterile. For mammals, esp cially humans, (assuming an approximate body weight f 70 kg) individual doses of from about 2 mg to about 400 mg of araalkanamide are acceptable. Individual doses of from about 50 mg to about 200 mg are preferrerd. Although frequency of administration will be determined by the duration of activity of the particular araalkanamide administered, which is variable, the araalkanamides are generally long-acting, and in some cases it may be possible to obtain effective relief by administering the composition as infrequently as once every 3-4 days.

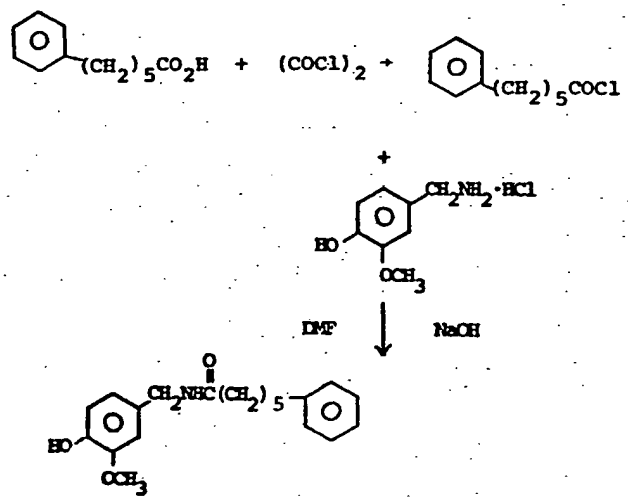
A preferred method of systemic application of the araalkanamides is through oral administration. For mammals, especially humans (assuming an approximate body weight of 70 kg) individual doses of from about 1 mg to about 900 mg of araalkanamide are acceptable. Individual doses of from about 50 mg to about 600 mg are especially preferred.

Topical administration can be used to reduce inflammation and produce local or systemic analgesia, through directly laying on or spreading a safe and effective amount of the araalkanamides, or composition containing a araalkanamide, on epidermal or epithelial tissue, including outer skin and oral, gingival, and nasal tissue. The amount of the pharmaceutical composition to be topically administered may vary from about 1mg/cm^2 to 5 mg/cm^2, depending upon such factors as the sensitivity, type and location of tissue to be treated, the composition and carrier (if any) to be administered, and the particular araalkanamide to be administered as well as the particular disorder to be treated and the extent to which systemic (as distinguished from local) effects are desired. The extent of systemic analgesia also depends upon such factors as the amount of araalkanamide, the area of tissue to be covered, and the ability of the araalkanamide composition to penetrate the skin tissues.

The following non-limiting Examples illustrate the compounds, compositions, and methods of treatment of the present invention.

Example I

N-vanillyl-6-phenylhexanamide was synthesized by the following method:



Specifically, 8 ml of oxalyl chloride was added to 3.e g of 6-phenylhexanoic acid in 10 ml of chloroform and refluxed at room temperature for 60 minutes. Excess solvent and oxalyl chloride was evaporated. In a separate flask, 3.0 g of vanillylamine hydrochloride was suspended in 30 ml of N,N-dimethylformamide (DMF). 6.24 ml of 5N NaOH was added, and the reaction was stirred at room temperature for 15-20 minutes. 20 ml of diethyl ether was added to the 6-phenylhexanoic acid chloride, and the resulting solution was added dropwise to the reaction mixture over a 20 minute time period. The resulting mixture was stirred at room temperature for 4 hours, then poured into 1 l of water, and extracted with 100 ml of ether. This process was repeated 3 times. Extracts were combined and washed with 50 ml 1N HCl, 50 ml saturated $NaHCO_3$, 50 ml H_2O, and 50 ml brine, dried over $MgSO_4$, and evaporated, 4.6 g of crude N-vanillyl-6-phenylhexanamide was obtained. The crude product was flash chromatographed with 60% EtOAC/hexane to provide 4.0 g of analytically pure product.

In the above example, N-vanillyl-2-phenylethanamide, N-vanillyl-3-phenylpropananmide, N-vanillyl-4-phenyl butyramide, N-vanillyl-5-phenylpentanamide, and N-vanillyl-7-phenylheptanamide were made by substituting the appropriate acids in the above systhesis.

Exampl II

A composition for parenteral adminstration is prepared by combining the following ingr dients:

N-vanillyl-6-phenylhexanamide	300 g
Ethyl oleate	980 ml
Benzyl alcohol	20 ml

The hexanamide is dissolved in the solution combining ethyl oleate and benzyl alcohol, sealed into airtight 5 ml ampoules, and sterilized by autoclaving. Injection of 1.5 ml of the contents of one of these ampoules intramuscularly into 65 kg human produces analgesia and reduces inflammation.

A substantially similar effect is obtained when N-vanillyl-6-phenylhexanamide is replaced with N-vanillyl-2-phenylethanamide, N-vanillyl-3-phenylpropanamide, N-vanillyl-4-phenylbutyramide, N-vanillyl-5-phenylpentanamide, or N-vanillyl-7-phenylheptanamide.

Example III

A composition for oral administration is prepared by combining the following ingredients:

N-vanillyl-6-phenylhexanamide	1.10 kg
Sesame oil	3.25 litres

The hexanamide is dissolved in the sesame oil with the aid of sonication and is packaged in soft gelatin capsules using methods known in the art. Two of the resulting capsules, each containing 225 mg of the composition, are administered to a 60 kg human, producing analgesia and reducing inflammation.

A substantially similar effect is obtained when N-vanillyl-6-phenylhexanamide is replaced with N-vanillyl-2-phenylethanamide, N-vanillyl-3-phenylpropanamide, N-vanillyl-4-phenylbutyramide, N-vannillyl-5-phenylpentanamide, or N-vannillyl-7-phenylheptanamide.

Example IV

A composition for oral administration is prepared by combining the following ingredients:

N-vanillyl-6-phenylhexanamide	360 g
Propylene glycol	1800 ml
Ethyl alcohol	175 ml
Distilled water	75 ml
Artifical Strawberry flavor	10 ml
FD&C Red #40	0.2 g

The above ingredients are combined to produce a syrup and are packaged under sterile conditions in 6 oz. bottles. One teaspoon of this formulation is administered to a 70 kg adult human, reducing inflammation and producing analgesia.

A substantially similar effect is obtained when N-vanillyl-6-phenylhexanamide is replaced with N-vanillyl-2-phenylethanamide, N-vanillyl-3-phenylpropanamide, N-vanillyl-4-phenylbutyramide, N-vanillyl-5-phenylpentanamide, or N-vanillyl-7-phenylheptanamide.

Example V

A composition for topical administration is prepared by combining the following ingredients:

N-vannillyl-6-phenylhexanamide	4 g
Propylene glycol	100 ml
Ethyl alcohol	100 ml

The hexanamide is melted to a liquid with slight warming and combined with the other ingredients. Application of 0.4 ml of the resulting liquid to a 80 cm^2 portion of the forearm of a 60 kg human reduces inflammation and produces analgesia.

A substantially similar effect is obtained when N-vanillyl-6-phenylhexanamide is replaced with N-vanillyl-2-phenylethanamide, N-vanillyl-3-phenylpropanamide, N-vanillyl-4-phenylbutyramide, N-vanillyl-5-phenylpentanamide, or N-vanillyl-7-phenylheptanamide.

Effectiveness in reducing inflammation and providing analgesia

Example VI

Six araalkanamide compositions were tested for anti-inflammatory activity using the croton oil induced mouse ear inflammation test.

Adult male Cox ICR mice, 20-30 g, were treated on the left ear at 20-28 hours prior to sacrifice and a second time 5-6 hours prior to sacrifice with 25 µl of a 1% ethanolic solution of the test compound. Four hours prior

to sacrifice both ears wer treated with 25 µl of a 2% solution of croton oil in acetone. Each animal was then placed in individual cages and given food and water *ad lib*. Animals were sacrificed by cervical dislocation and both ears removed. From thes ears, 0.38 cm^2 punch biopsies were taken from the central portion and each biopsy weighed on a Cahn electrobalanc .

For each test substance, a group of 10 animals was used. Control groups either had both ears treat d with croton oil or just the right ear. It was experimentally determined that a value of 11.0 mg could be assumed for a punch biopsy from a normal untreated ear and still be within the experimental error of the test. Therefore, for the calculation of percent inhibition, a value of 11.0 mg was used.

$$\frac{\text{Weight Right Ear} - \text{Weight Left Ear}}{\text{Weight Right Ear} - \text{Weight Control Ear (11.0 mg)}} \times 100$$

This calculation is valid only when no systemic effects are noted as evidenced by comparison of right ears of treated and control groups.

Statistical significance at the 95% confidence level was determined by the paired t test.

Results were graphed in order to demonstrate the relationship of the value of n_4 (alkyl chain length) to anti-inflammatory activity.

Compound	*% Inhibition*
N-vanillyl-1-phenylmethanamide	16.8 ±15.2
N-vanillyl-2-phenylethanamide	30.2 ±27.2
N-vanillyl-3-phenylpropanamide	33.1 ±15.7
N-vanillyl-4-phenylbutyramide	40.9 ±30.0
N-vanillyl-5-phenylpentanamide	56.4 ±20.9
N-vanillyl-6-phenylhexanamide	57.6 ±32.7
N-vanillyl-7-phenylheptanamide	46.2 ±28.7

These results show that the araalkanamide compositions tested do in fact have anti-inflammatory activity. They also demonstrate the effect of the alkyl chain length on the strength of the anti-inflammatory activity. As is evident from the Figure, anti-inflammatory activity increases as n_4 increases from 0 to 5, then decreases slightly at n_4=6.

Example VII

Four araalkanamide compositions were tested for analgesic and anti-inflammatory activity using the phenylquinone writhing assay.

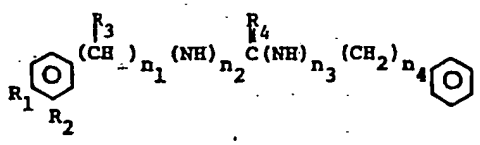
Groups of eight male mice weighing between approximately 25 and 30 g were dosed orally by gavage with 20 mg/kg of the composition to be tested. Indentical groups of mice were dosed subcutaneously with a vehicle control composition composed of 10% ethanol, 10% Tween 80 (polyoxyethylene (20) sorbitan monooleate) and 80% saline. Three hours after this initial administration, the mice were injected intraperitoneally with a 0.2% solution of phenylbenzoquinone in aqueous ethanol. The ability of the analesic compositions tested to relieve the discomfort induced was measured by counting the number of abdominal contractions, or "writhes", occurring in each mouse during a 10 minute period beginning 10 minutes after injection of the phenylbenzoquinone solution.

Compound	*Writhes/10 minutes*
N-vanillyl-2-phenylethanamide	12.9 ± 1.2
N-vanillyl-4-phenylbutyramide	16.6 ± 3.4
N-vanillyl-5-phenylpentanamide	1.5 ± 1.0
N-vanillyl-7-phenylheptanamide	0.0 ± 0.0
Vehicle control	21.0 ± 3.8

These results show that the araalkanamide compositions tested exhibit anti-inflammatory/analgesic activity similar to that of the aspirin-like compositions.

CLAIMS

1. Araalkanamide compounds, and pharmaceutically-acceptable salts thereof, of the formula:



wherein n_1 is 0 or 1, n_2 is 0 or 1, n_3 is 0 or 1, n_4 is an integer between 0 and 12, $n_2+n_3=1$, R_1 is selected from

the group consisting of H, OH, and a short-chain ester, R_2 is selected from the group consisting of H, OH, OCH_3, and OCH_2CH_3, R_3 is H or CH_3, and R_4 is O or S.

2. Araalkanamide compounds, and pharmaceutically-acceptable salts thereof, according to Claim 1, wherein n_1 is 1, n_2 is 1, and n_3 is 0.

3. Araalkanamide compounds, and pharmaceutically-acceptable salts thereof, acccording to Claim 2, wherein R_3 is H.

4. Araalkanamide compounds, and pharmaceutically-acceptable salts thereof, according to Claim 3, wherein R_4 is 0.

5. Araalkanamide compounds, and pharmaceutically-acceptable salts thereof, according to Claim 4, wherein R_1 is OH or a short-chain ester and R_2 is OH or OCH_3.

6. Araalkanamide compounds, and pharmaceutically-acceptable salts thereof, according to Claim 5, wherein R_1 is OH and R_2 is OCH_3.

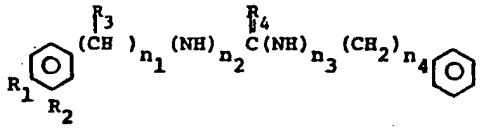
7. Araalkanamide compounds, and pharmaceutically-acceptable salts thereof, according to Claim 6, wherein n_4 is an integer between 0 and 8.

8. Araalkanamide compunds, and pharmaceutically-acceptable salts thereof, according to Claim 7, wherein n_4 is an integer between 0 and 6.

9. Araalkanamide compounds, and pharmaceutically-acceptable salts thereof, according to Claim 8, wherein n_4 is an integer between 4 and 6.

10. A composition for reducing inflammation and producing analgesia in humans or lower animals comprising:

(a) a safe and effective amount of araalkanamide compound of the formula



wherein n_1 is 0 or 1, n_2 is 0 or 1, n_3 is 0 or 1, n_4 is a number between 0 and 12, $n_2+n_3=1$, R_1 is selected from the group consisting of H, OH, and a short-chain ester, R_2 is selected from the group consisting of H, OH, and OCH_3, and OCH_2CH_3, R_3 is H or CH_3, and R_4 is O or S, or a pharamceutically-acceptable salt thereof; and

(b) a pharmaceutically-acceptable carrier.

11. A composition, according to Claim 10, wherein n_1 is 1, n_2 is 1, and n_3 is 0.

12. A composition, according to Claim 11, wherein R_3 is H.

13. A composition, according to Claim 12, wherein R_4 is O.

14. A composition, according to Claim 13, wherein R_1 is OH or a short-chain ester and R_2 is OH or OCH_3.

15. A composition, according to Claim 14, wherein R_1 is OH and R_2 is OCH_3.

16. A composition, according to Claim 15, wherein n_4 is an integer between 0 and 8.

17. A composition, according to Claim 16, wherein n_4 is an integer between 0 and 6.

18. A composition, according to Claim 17, wherein n_4 is an integer between 4 and 6.

19. A composition, according to Claim 10, for parenteral administration, comprising at least about 90%, by weight, of said pharmaceutically-acceptable carrier.

20. A composition, according to Claim 10, for oral administration, comprising from about 25% to about 50% by weight, of said araalkanamide.

21. A composition, according to Claim 10, for topical administration, comprising from about 1% to about 5%, by weight, of said aralkanamide.

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